Appl. No. 09/771,277

Amdt. dated January 6, 2004

Reply to Office Action of May 2, 2003

#### REMARKS

This Amendment is submitted in response to the Office Action mailed September 5, 2003. At that time, claims 1-50 were pending in the application. The Office Action indicated that claim 27 contained allowable subject matter. Most of rejections set forth in the previous Office Action have been withdrawn. However, the Examiner maintained the rejection of claims 1-22, 24-26, and 29-50 under § 103(a) as being unpatentable over the article written by Hanning et al. (hereinafter "Hanning") in view of the article written by Beale and Sudmeier (hereinafter "Beale") and the rejection of claim 23 under § 103(a) as being unpatentable over Hanning in view of Beale and in further view of the article written by Li et al (hereinafter "Li"). Claim 28 was newly rejected under § 103(a) as being unpatentable over Hanning in view of Beale and further in view of the article written by Kim et al (hereinafter "Kim").

By this amendment, claims 3, 4, 23, and 29 were canceled, and claims 1, 5, 11-14, 19, 34, and 40 have been amended. The claims were amended to recite that the excitation source rasters an excitations beam onto the capillary along part or all of the length of the capillary. Rastering is discussed in the specification at pages 6, 9, 10, 13, 16, 21, and 22, shown in Figure 1 by arrows A and B, and recited in original claims 29, 40, 41, and 50. Accordingly, claims 1, 5-22, 24-28, and 30-50 are presented for reconsideration by the Examiner.

Telephonic Interview. Applicants' attorney expresses appreciation to Examiner Starsiak for discussing this application on November 14, 2003 and November 18, 2003. During those interviews, some proposed amendments to the claims were discussed which included amending claims 1 and 19 to recite that the excitation beam is rastered onto the capillary along part or all of the length of the capillary. It was agreed that the Beale secondary reference does not disclose the concept of rastering the excitation beam along the capillary and that Beale discloses an apparatus in which the excitation beam (through a confocal detection system) is kept stationary and that the capillary (mounted onto a movable table) is moved relative to the excitation beam. It was further

agreed that the Beale reference generally discloses advantages that are obtained from "scanning the entire length of the capillary."

Another prior art reference of record, Kim et al., Analytical Chemistry, Vol. 68, No. 5, March 1, 1996, discloses a postelectrophoresis capillary scanning method in which the capillary is scanned by moving the capillary through a stationary excitation beam and detector system. Neither the Examiner nor the Applicants' attorney was aware of prior art which discloses rastering the excitation beam along a stationary electrophoresis capillary. It was also agreed that the capillary electrophoresis detection system of Beale is substantially different than the capillary electrophoresis detection system of the primary reference, Hanning, and that of the claimed invention. Hanning and the claimed invention both disclose capillary electrophoresis systems in which the capillary is a light wave guide and the fluorescent light emitted is detected at the end of the capillary and not transversely as with Beale. An unresolved issue from the telephonic interviews was the appropriate scope of Beale's disclosure.

Claim Rejections – 35 U.S.C. § 103. The Office Action rejected claims 1-22, 24-26, and 29-50 under 35 U.S.C. § 103(a) as being unpatentable over Hanning in view of Beale. The Applicants respectfully traverse this rejection and submit that the claimed invention would not have been obvious from the combined disclosure of Hanning and Beale.

Both Hanning and Beale refer to the capillary electrophoresis work of Mathies. Hanning, page 3423, right column, states:

Mathies et al. have developed a *scanning* confocal microscope for capillary array detection. This scheme has *certain drawbacks*, *such as the need for scanning optics* and the critical alignment and positioning required due to the shallow focal depth of the objective. (emphasis added).

Beale, page 3367, right column, states:

<sup>&</sup>lt;sup>1</sup> See references 5-6 in Beale and references 30-37 in Hanning.

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The system we present is similar to the capillary array electrophoresis system described by Mathies and co-workers<sup>5,6</sup> for continuously monitoring the outlet ends of several capillaries in a bundle. We have adapted Mathie's geometry to scan the entire length of a single capillary.

The only difference between Mathies' confocal detection system and Beale's confocal detection system is that Beale uses the scanning confocal system to scan the length of a single capillary by moving the capillary and fixing the confocal detection system, while Mathies used the same confocal system to scan transversely across an array of fixed capillaries. Nevertheless, the limitations recognized by Hanning still remain, i.e., the need for scanning optics and critical alignment and positioning, which were not addressed by Beale. Therefore, one skilled in the art would not have been motivated to modify the Hanning's liquid core waveguide device to be a scanning system according to Beale because Hanning specifically rejected a scanning system because of "the need for scanning optics and the critical alignment and positioning required."

Moreover, Beale's manuscript appeared in the literature one year prior to Hanning's manuscript. Hanning's intention was to provide a faster, more sensitive, simpler, high throughput method for DNA sequencing. Yet Hanning was not motivated to use a scanning source with his liquid core waveguide system, because the belief at the time was that such a scanning source would be too complicated to implement because of the drawbacks identified above.

#### A Prima Facie Case of Obviousness Has Not Been Established

A prima facie case of obviousness is established only if the Examiner shows that (1) there is some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art teaches or suggests all of the claim limitations. See MPEP 2142.

1. There is Insufficient Teaching Or Motivation To Combine Hanning and Beale. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the there some teaching that suggests the desirability of the combination. See e.g., In re Mills, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). In other words, even if all of the claimed elements are disclosed by the references, the claimed invention cannot be said to be obvious without some objective evidence of record that indicates why one of ordinary skill in the art would have been prompted to combine the teachings of the references and arrive at the claimed invention. See MPEP § 2143.01; In re Lee, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002).

In the present case, Beale teaches a method for detecting fluorescent emissions in capillary electrophoresis systems by using a confocal microscope that scans the length of the capillary. See Beale, page 3367. Such a detection system is based upon and employs the scanning confocal microscope system taught by "Mathias and co-workers for continuously monitoring the outlet ends of several capillaries in a bundle." Id. In Beale, the scanning is achieved by moving the capillary on a traverse stage and presenting it to a fixed point light source and detection system. If the Hanning capillary were "scanned" according to the teachings of Beale, Hanning's Teflon coating would have to be removed for fluorescence detection to occur, otherwise the Teflon coating would prevent the confocal point light source and detection system from functioning. If Hanning's Teflon coating were removed, it would obviate the principle of internal reflection using a liquid core waveguide, which Hanning teaches, thus destroying the function of Hanning's device.

MPEP 2143.01 states that "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). In this case, modifying the device of Hanning such that the Hanning capillary is "scanned" as taught by Beale would not merely change the principle of operation of Hanning's device, it would destroy it.

Moreover, in order for Hanning to use a liquid core waveguide and a confocal detection system, the detector would need to be moved to one end of the capillary, which would obviate the confocal arrangement which Beale teaches, plus with the capillary moving (as taught by Beale), the confocal detection system would require continuously focusing objectives, which would be an impractical situation.

From the foregoing, Applicants respectfully submit that neither Hanning nor Beale suggests the desirability of the combination, because to do so would "change the principle of operation of the prior art invention being modified." Accordingly, as Hanning dismisses *scanning* confocal microscope systems as being inadequate and limited, the Applicants submit that there is no teaching that would have led one of ordinary skill to combine Hanning and Beale. As such, the combination of Hanning and Beale may not be used to reject the present claims under § 103(a). Withdrawal of this rejection is respectfully requested.

2. All the claim limitations are not taught by the prior art. "To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03. In this case, claim 1 recites "an excitation source for rastering an excitation beam onto the capillary along part or all of the length of the capillary" and "determining the location of particles within the capillary based upon the location of the rastered excitation beam." The specification discusses rastering at pages 6, 9, 10, 13, 16, 21, and 22, and shown in Figure 1 by arrows A and B. The term rastering refers to moving the excitation beam along the capillary. It implies the capillary is stationary, while the excitation beam moves along its length. Neither Hanning nor Beale discloses "rastering an excitation beam onto the capillary" and "determining the location of particles within the capillary based upon the location of the rastered excitation beam." Thus, "all the claim limitations" are not "taught or suggested by the prior art," and prima facie obvious is not established.

#### 3. The invention must be viewed as a whole. MPEP 2144.08 states:

When evaluating the scope of a claim, every limitation in the claim must be considered. See, e.g., *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995). However, the claimed invention may not be dissected into discrete elements to be analyzed in isolation, but must be considered as a whole. See, e.g., *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1983) ("treating the advantage as the invention disregards the statutory requirement that the invention be viewed 'as a whole'").

During the telephonic interviews, Applicants' attorney and the Examiner agreed that Beale discloses some advantages from scanning the entire length of the capillary, such as quicker analysis time and the possibility of using a shorter effective column length. The Examiner suggested that these advantages may support a broad interpretation of Beale, i.e., that Beale discloses the desirability of any capillary scanning technique regardless of whether the technique involves a stationary excitation source and detection system with a moving capillary or a stationary capillary with a moving excitation source. However, the Applicants do not claim to have invented the advantages from scanning the entire length of the capillary. Applicants claim particular apparatus and methods of capillary electrophoresis which include structures and method steps that are not disclosed or suggested by the cited prior art individually or in combination. The invention must be examined as a whole; as noted above, "treating the advantage as the invention disregards the statutory requirement that the invention be viewed 'as a whole." The fact that Beale discloses certain advantages of scanning a capillary, but in a different manner than the claimed invention, does not mean that the claimed invention would have been obvious. The claimed invention must be examined, not the advantages obtained from the claimed invention. Since the claimed invention as a whole is not taught or suggested by the combined prior art, Applicants submit that prima facie obviousness is not established.

4. Disclosure of genus does not establish prima facie obviousness of claimed species.

MPEP 2144.08 states: "The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)." In this case, the Beale reference discloses one technique of "scanning" a capillary by mounting the capillary on a movable table and utilizing a stationary confocal detection system. This is essentially one "species" within the general "genus" or field of "scanning." During the telephonic interviews, the Examiner suggested that the Beale's disclosure of one specific species may be considered a general disclosure of the entire field (or genus) of capillary electrophoresis scanning. The rejected claims are drawn to a different "species" or technique of scanning a capillary. According to the rule set forth in *In re Baird*, Applicants respectfully submit that Beale's general disclosure of scanning a capillary does not by itself establish *prima facie* obviousness of the claimed scanning apparatus and method.

In view of the foregoing, Applicants submit that claims 1-22, 24-26, and 29-50 would not have been obvious from the combined disclosure of Hanning and Beale. Withdrawal of the rejection and allowance of these claims is respectfully requested.

#### Rejection of claim 23 under 35 U.S.C. § 103(a)

Claim 23 was rejected under §103(a) as being unpatentable over Hanning in view of Beale and in further view of the article written by Li. The Li reference was cited for the purpose of disclosing the use of a fiber optic to transmit light from the end of the capillary to a photodiode. The Li reference fails to disclose those claim features that are lacking in the Hanning and Beale references, including, but not limited to, the rastering feature discussed above. Therefore, Applicants submit that claim 23 would not have been obvious from the combination of references. Withdrawal of the rejection is respectfully requested.

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Rejection of claim 28 under 35 U.S.C. § 103(a)

Claim 28 was newly rejected under § 103(a) as being unpatentable over Hanning in view

of Beale and further in view of Kim. The Kim reference was cited for the purpose of disclosing

the use of a narrow band pass filter. The Kim reference fails to disclose those claim features that

are lacking in the Hanning and Beale references, including, but not limited to, the rastering

feature discussed above. Therefore, Applicants submit that claim 28 would not have been

obvious from the combination of references. Withdrawal of the rejection is respectfully

requested.

CONCLUSION

In view of the foregoing, the Applicants submit that claims 1, 5-22, 24-28, and 30-50 are

in a condition for immediate allowance. If there are any remaining issues preventing allowance

of the pending claims that may be clarified by telephone, the Examiner is requested to call the

undersigned.

Respectfully submitted,

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Claim 1 (currently amended): A device for separating and detecting particles comprising: a capillary having a first end and a second end, the capillary filled with a buffer solution, the capillary having a coating that transforms the capillary into a light wave guide;

an electrical source for applying a voltage across the capillary, the voltage causing the particles to travel from a first location within the capillary to a second location within the capillary, and

an excitation source for rastering an excitation beam onto the capillary along part or all of the length of the capillary, such that when a fluorescently labeled particle is positioned within the capillary, the fluorescently labeled particle emits light after excitation with the excitation beam; and

a <u>light</u> detector <u>positioned</u> at one of the <u>first</u> or second <u>ends</u> of the <u>capillary</u> to collect <u>fluorescent light emitted from the excited fluorescently labeled particles</u> for determining the location of particles within the capillary <u>based upon the location of the rastered excitation beamthe detector eapable of determining the location of particles at more than one position along the length of the capillary.</u>

Claim 2 (original): The device of claim 1, further comprising a first reservoir in fluid communication with the first end of the capillary, the first reservoir configured to contain buffer solution and a second reservoir in fluid communication with the second end of the capillary, the second reservoir configured to contain buffer solution

Claim 3 (canceled): The device of claim 1, further comprising a fluorescent label attached to the particles.

Claim 4 (canceled): The device of claim 3, wherein the detector further comprises an excitation source for directing an excitation beam onto the fluorescently labeled particles within the capillary, the fluorescently labeled particles omitting light after excitation with the excitation beam.

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Claim 5 (currently amended): The device of claim 1 [[4]], wherein the <u>light</u> detector further comprises a fiber optic coupled end-on to the capillary a light detector positioned to collect fluorescent light emitted from the excited-fluorescently labeled particles.

Claim 6 (original): The device of claim 5, wherein the light detector comprises low-level light detection electronics.

Claim 7 (previously amended): The device of claim 5, wherein the coating on the capillary that transforms the capillary into a light wave guide directs the fluorescent light toward the light detector.

Claim 8 (previously amended): The device of claim 1, wherein the coating has a refractive index number in the range from about 1.1 to about 1.4.

Claim 9 (previously amended): The device of claim 1, wherein the coating has a refractive index number of about 1.3.

Claim 10 (previously amended): The device of claim 8, wherein the coating is polytetrafluoroethylene.

Claim 11 (currently amended): The device of claim 1 [[4]], wherein the excitation beam has a power in the range from about 1 mW to about 1000 mW.

Claim 12 (currently amended): The device of claim  $\underline{1}$  [[4]], wherein the excitation beam has a width in the range from about 5  $\mu m$  to about 1000  $\mu m$ .

Claim 13 (currently amended): The device of claim  $\underline{1}$  [[4]], wherein the light detector can distinguish between more than one color of fluorescent light.

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Claim 14 (currently amended): The device of claim 1 [[4]], wherein the light detector may be placed at either end or both ends of the separation capillary.

Claim 15 (currently amended): The device of claim 1, further comprising a plurality of capillaries.

Claim 16 (previously amended): The device of claim 1, wherein the buffer solution comprises a gel sieving material, a surface deactivating agent, and a buffer selected from the group consisting of tris-boric acid EDTA, potassium tartrate, and tris-acetate EDTA.

Claim 17 (original): The device of claim 16, wherein the gel sieving material is selected from the group consisting of poly(ethylene glycol), poly(vinyl alcohol), hydroxy propyl methyl cellulose, hydroxyethylcellulose, and linear polyacrylamide.

Claim 18 (original): The device of claim 16, wherein the surface deactivating agent is poly(vinylpyrrolidone).

Claim 19 (currently amended): A device for separating and detecting particles comprising:

a capillary having a first end and a second end the capillary filled with a buffer solution, the capillary having a coating that transforms the capillary into a light wave guide;

a first reservoir in fluid communication with the first end of the capillary, the first reservoir configured to contain buffer solution;

a second reservoir in fluid communication with the second end of the capillary, the second reservoir configured to contain buffer solution;

an electrical source for applying a voltage across the capillary, the voltage causing a fluorescently labeled particle positioned within the capillary to travel from a first location within the capillary to a second location within the capillary;

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an excitation source for directing an excitation beam onto the capillary, such that when a fluorescently labeled particle is positioned within the capillary, the fluorescently labeled particle emits light after excitation with the excitation beam;

the excitation source capable of exciting fluorescently labeled particles at more than one position along the capillary wherein the excitation beam is rastered along part or all of the length of the capillary; and

a light detector positioned to collect fluorescent light emitted from excited fluorescently labeled particle located within the capillary, wherein the light detector comprises a fiber optic coupled end-on to the capillary.

Claim 20 (previously amended): The device of claim 19, wherein the coating on the capillary that transforms the capillary into a light wave guide is capable of directing the fluorescent light toward the light detector.

Claim 21 (original): The device of claim 19, wherein the coating has a refractive index of about 1.3.

Claim 22 (original): The device of claim 19, wherein, the coating is polytetrafluoroethylene.

Claim 23 (canceled): The device of claim 19, wherein the light detector comprises a fiber optic coupled end on to the capillary.

Claim 24 (original): The device of claim 19, wherein the light detector comprises low-level light detection electronics.

Claim 25 (original): The device of claim 24, wherein the low-level light detection electronics are selected from the group consisting of photomultipliers, photodiodes, and CCD cameras.

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Claim 26 (original): The device of claim 24, wherein the light detector further comprises an optical filter, prism, grating, or light spectrometer positioned between the light detection electronics and the capillary for filtering incident light, and the resulting fluorescence.

Claim 27 (original): The device of claim 26, wherein the optical filter comprises a high band pass filter for filtering light with a wavelength greater than about 500 nm and a notch filter.

Claim 28 (original): The device of claim 26, wherein the optical filter comprises a narrow band pass filter which filters light other than light with a wavelength corresponding to the wavelength of the light emitted from the fluorescent label,  $\pm 10$  nm.

Claim 29 (canceled): The device of claim 19, wherein the excitation beam is rastered along part or all of the length of the capillary.

Claim 30 (original): The device of claim 19, wherein the excitation beam has a power in the range from about 1 mW to about 1000 mW.

Claim 31 (original): The device of claim 19, wherein the excitation beam has a width in the range from about 5  $\mu m$  to about 1000  $\mu m$ .

Claim 32 (original): The device of claim 19, wherein the light detector can distinguish between more than one color of fluorescent light.

Claim 33 (original): The device of claim 19, further comprising a plurality capillaries.

Claim 34 (currently amended): The device of claim 19, wherein the buffer solution comprises a gel sieving material, a surface deactivating agent, and a buffer selected from the group consisting of tris-boric acid EDTA, potassium tartrate, and tris-acetate EDTA.

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Claim 35 (original): The device of claim 34, wherein the gel sieving material is selected from the group consisting of poly(ethylene glycol), poly(vinyl alcohol), hydroxy propyl methyl cellulose, hydroxyethylcellulose, or linear polyacrylamide.

Claim 36 (previously amended): The device of claim 34, wherein the surface deactivating agent is poly(vinylpyrrolidone).

Claim 37 (original): The device of claim 34, wherein the gel sieving material is at a concentration in the range from about 0.1% to about 5% and has a viscosity in the range from about 0.5 cp to about 50 cp at room temperature.

Claim 38 (original): The device of claim 19, wherein the capillary has a length in the range from about 5 cm to about 100 cm.

Claim 39 (original): The device of claim 19, wherein the capillary has a length of about 20 cm.

Claim 40 (currently amended): A method for separation and sizing of particles in short channels by capillary electrophoresis comprising:

obtaining a sample of particles;

fluorescently labeling the particles;

loading the sample into a device for separating and sizing particles, the device comprising a capillary having a first end and a second end filled with a buffer solution, the capillary having a coating that transforms the capillary into a light wave guide, a first reservoir in fluid communication with the first end of the capillary, the first reservoir configured to contain the buffer solution, a second reservoir in fluid communication with the second end of the capillary, the second reservoir configured to contain the buffer solution, an electrical source for applying a voltage across the capillary, the voltage causing the fluorescently labeled particles to travel from

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a first location within the capillary to a second location within the capillary, an excitation source for directing an excitation beam onto fluorescently labeled particles within the capillary, the fluorescently labeled particles emitting fluorescent light after excitation with the excitation beam, the excitation source capable of exciting the fluorescently labeled DNA particles at more than one position along length of the capillary, and a light detector positioned to collect the fluorescent light emitted the excited fluorescently labeled particle;

applying the voltage across the capillary;
rastering the excitation beam on the capillary;
monitoring fluorescent light in the light detector; and
comparing the position of the excitation beam on the capillary when light is collected by
the light detector to determine the position of the particles in the capillary; and
determining the relative size of the particles from the determined position.

Claim 41 (currently amended): The method of claim 40, wherein the device further comprises at least one additional capillary having a first end and a second end, the at least one additional capillary filled with buffer solution and having a coating that transforms the additional capillary into a light wave guide, the at least one additional capillary being in fluid communication with the first and second reservoirs, the method further comprising obtaining a second sample of particles of a known size, fluorescently labeling the particles of the second sample, applying the voltage across the at least one additional capillary, rastering the excitation beam on the at least one additional capillary, monitoring the collection of fluorescent light in the light detector; and comparing the position of the excitation beam on the capillary when light is collected by the light detector to determine the position of the particles of known size, comparing the position of the particles of known size to the position of the sample particles to determine the size of the sample particles.

Claim 42 (original): The method of claim 41, wherein the voltage is in the range of about 4,000 V to about 20,000 V dc.

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Claim 43 (original): The method of claim 41, wherein the capillary has a length in the range of about 5 cm to about 100 cm.

Claim 44 (original): The method of claim 43, wherein the length is in the range of about 10 cm to about 25 cm.

Claim 45 (original): The method of claim 43, wherein the length is in the range of about 20 cm.

Claim 46 (original): The method of claim 41, wherein the particle is selected from the group consisting of a nucleic acid, a protein, inorganic ions, and organic ions, and neutral species.

Claim 47 (previously amended): The method of claim 41, wherein the coating on each of the capillaries that transforms the capillaries into a light wave guide directs the fluorescent light toward the light detector.

Claim 48 (previously amended): The method of claim 41, wherein the coating has a refractive index of about 1.3.

Claim 49 (previously amended): The method of claim 41, wherein the coating comprises polytetrafluoroethylene.

Claim 50 (original): A method for sequencing DNA comprising:

obtaining a sample of DNA to be sequenced;

running a dideoxy sequencing reaction on the DNA sample, the sequencing reaction comprising a separate reaction mixture for each nucleotide type, each reaction mixture comprising a different flourescent label, each reaction mixture run to form a separate reaction product;

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pooling the reaction products of the reaction mixtures;

loading the pooled reaction products into a device for separating and detecting particles, the device comprising a capillary having a first end and a second end filled with a buffer solution, a first reservoir in fluid communication with the first end of the capillary, the first reservoir configured to contain the buffer solution, a second reservoir in fluid communication with the second end of the capillary, the second reservoir configured to contain the buffer solution, an electrical source for applying a voltage across the capillary, the voltage causing the fluorescently labeled reaction products to travel from a first location within the capillary to a second location within the capillary, an excitation source for directing an excitation beam onto the fluorescently labeled reaction products within the capillary, the fluorescently labeled reaction products emitting fluorescent light after excitation with the excitation beam, the excitation source capable of exciting the fluorescently reaction products at more than one position along length of the capillary, and a light detector positioned to collect the fluorescent light emitted the excited fluorescently labeled reaction products;

applying the voltage across the capillary;
rastering the excitation beam on the capillary;
monitoring the collection of fluorescent light in the light detector; and
comparing the position of the excitation beam on the capillary to the color of light
detected by the light detector to determine the position of a corresponding nucleotide within the
DNA sample.